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Dated 22 August 2003

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1. Your reference — P31928-/NBW/BPU

2. Patent application number (The Patent Office will fill in this part) — 02 AUG 2002 — 0217930.7

3. Full name, address and postcode of the or of each applicant (underline all surnames)

   Glycologic Limited
   Glasgow Caledonian University
   School of Biological and Biomedical Sciences
   City Campus, Cowcaddens Road, Glasgow

   08438209001

   Patents ADP number (if you know it) — 1198015

   If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — "A Chemical Carrier"

5. Name of your agent (if you have one) — Murgitroyd & Company

   "Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

   Scotland House
   165-169 Scotland Street
   Glasgow
   G5 8PL

   Patents ADP number (if you know it) — 1198015

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country	Priority application number (if you know it)	Date of filing (day / month / year)

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:
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Description	24
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Request for preliminary examination and search (Patents Form 9/77)	
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11. I/We request the grant of a patent on the basis of this application

Signature Murgitroyd & Company

Date 1 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

PURDY, Hugh Barry 0141 307 8400

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A Chemical Carrier

The invention relates to solid and liquid formulations comprising an active agent and a carrier for the active agent.

Starches are comprised of α-glucans (amylose and amylopectin in variable proportions, amounting to ~82 to 89%), moisture (~11 to 17%), lipids (cereal starches only, <1.5%) and protein (~0.5%) with some α-glucan phosphate-esters (especially in potato amylopectin). Plants produce starches in different sizes and shapes which reflect the botanical origin. In rice starch for example, the granules are <5μm in diameter while in potato starch they may exceed 50μm. The amylose fraction of starches comprise predominantly linear α-(1-4)-glucan molecules with a molecular weight of ~0.25 million Daltons. Amylopectin molecules are much larger with a molecular weight of a few million Daltons and comprise a heavily branched structure of small unit

chains (~15 to 80 glucose units long). The unit chains are like amylose α-(1-4)-glucans (~95% of bonds) but are linked together by α-(1-6) bonds (~5%). Native starch granules contain double helices of amylopectin which associate together to form crystalline laminates which are interspersed with amorphous amylopectin and amylose chains.

The properties of native starches from different botanical origins may be modified by genetic, chemical, enzymatic and/or physical processing. During the last few centuries, novel mutations have been developed where the ratio of amylose to amylopectin in the starches has been modified to create 'high amylose' starches where the α-glucan fraction may represent >70% amylose (<30% amylopectin) and 'waxy' starches where the amylopectin fraction may represent >70% amylopectin (<30% amylose). Modern methods of 'transgenic' technology may also be used to create novel glucans within starch granules with different chain lengths, distributions and potentially even sugar residues other than glucose. Chemical methods have been used to enhance the properties of starch granules where residues may be added by chemical bonding, stabilisation may be achieved by cross-linking or molecular weight may be reduced by hydrolysis (with for example acids). Glucose syrups may be made from starches by acid hydrolysis but are more often made by enzymatic hydrolysis (below). Here, amylases (specifically α-amylase) and amyloglucosidase can be used to produce syrups with variable proportions of

different chain lengths and sugars (glucose and maltose). Physically, starches may be pre-gelatinised (heated in water to remove crystallinity and dried to make 'instant' products) or damaged (e.g. milled to remove ordered structure) to moderate their functionality also.

Dextrins represent hydrolytic products of starches. They are produced using a number of approaches as discussed above.

Extensive acid hydrolysis may be used to produce low molecular weight dextrins (<degree of polymerisation, DP, ~20) where they may be branched or linear, together with sugars in variable proportions. The extent of hydrolysis is described relative to the amount of reducing power compared to a standard dextrose solution (dextrose equivalence, DE). When glucose syrups are purchased they are defined in terms of DE which suit specific applications. These products are used extensively in the food industry in confectionery, desserts, drinks, cakes and pastries etc. where there is a requirement for sweetness and product 'body'. In the pharmaceutical industry there is a similar need for glucose syrups in for examples pastilles and tinctures with a need for pure glucose (dextrose) in for example intra-venous products.
Less extensive acid hydrolysis of starches (with some transglucosidation and repolymerisation) is achieved by treating dry starches with acids and heating at high temperatures. These dextrin products

are described as 'pyrodextrins' which readily disintegrate in water and progressively solubilise. They are classified as 'white', 'yellow' or 'British Gums'. These dextrins have varying disintegrating and solubilising characteristics and have specific applications as for example tablet excipients.

Cyclodextrins are ring forms of dextrin oligomers. The rings may contain six, seven or eight glucose residues forming a hydrophobic core and hydrophilic exterior. Hydrophobic residues (e.g. drugs) may be located inside these cores and provide a vehicle for drug delivery. A number of manufacturers prepare cyclodextrins and their industrial utilisation is quite well established (below).

Unlike the pyrodextrins, α-(limit)-dextrins generated by α-amylase hydrolysis are not employed as high molecular weight products (where there is limited hydrolysis), either in the food or pharmaceutical sectors. Similarly, β-limit dextrins produced by hydolysis of soluble starches (generating the dextrins from amylopectin and maltose sequentially from the α-glucan non-reducing ends) are not used extensively in these industries. The α-limit dextrins become more soluble as hydrolysis is extended which, although random, is initially restricted to starch amorphous regions. The β-limit dextrins are highly soluble as exterior chains of amylopectin have been hydrolysed (to maltose) leaving short stubs attached to the (high

molecular weight) branched limit-dextrin residues. β-limit dextrins are not at present commercially available.

According to the National Starch web directory (http://www.foodstarch.com/directory), a dextrin may be defined as:

'Dextrins are starch hydrolysis products obtained in a dry roasting process either using starch alone or with trace levels of acid catalyst. The products are characterised by good solubility in water to give stable viscosities. Four types exist: White, Yellow, British Gums and Solution-stable dextrins.'

Note that in reference to this commercially accepted term, citations in patents referring to the use of 'dextrins' (e.g. Gregory (1983) and Gole et al (1994), as discussed below) exclude β-limit dextrins since they can only be produced in the solubilised and not the dry state.

The properties of different dextrins are, as discussed above, very different in terms of their chemical and physical properties. They also have different properties with respect to their potential to be hydrolysed by different enzymes. Comparisons are broadly made as follows:

Comparison of properties of different dextrins

Note that commercial 'dextrins are produced by heating starches in the presence of a very small amount of acid which induces hydrolysis, transglucosidation and repolymerisation.

Dextrin	Product characteristics	Chemical properties	Physical properties
β-limit dextrin [*Not a dextrin according to common commercial/ industrial usage of the term, see definition above*]	White powder produced by hydrolysing solubilised amylopectin (from starch) with β-amylase	Molecular weight of dextrin ~ 50% that of amylopectin. Incorporates no amylose residues. Maltose would be present (from amylose and amylopectin hydrolysis) unless removed by for example dialysis or chromatography.	Soluble powder with no granular or crystalline form - i.e. amorphous.
British Gums [*True commercial dextrin*]	Dextrin, usually yellow or brown and darker than standard 'yellow dextrins' below. Powder form produced by roasting ~ dry starch at high temperatures at ~ neutral pH.	Hydrolysed starches incorporating residues of amylose and amylopectin which will incorporate some transglucosidation and repolymerisation	Dark coloured and relatively soluble - especially when heated - in water.
Maltodextrin [*Not a dextrin*	Produced from extensive acid or	Branched dextrins comprising	Soluble dextrins with reducing power

according to common commercial/ industrial usage of the term, see definition above]	α-amylase (α-limit dextrin) hydrolysis of starch. Component of glucose syrups.	α-(1-4) and α-(1-6) bonds. Low molecular weight (degree of polymerisation, DP, < ~ 20) soluble branched product.	much greater than starch polysaccharides but less than free sugars. Dextrose equivalence (DE), 5-20.
White Gums [*True commercial dextrin*]	Dextrin, usually ~ white. Powder form produced by roasting ~ dry starch at relatively low temperatures at low pH.	Hydrolysed starches incorporating residues of amylose and amylopectin which will incorporate some transglucosidation and repolymerisation	Light coloured and relatively soluble - especially when heated - in water.
Yellow Gums (also referred to as Canary Gums) [*True commercial dextrin*]	Dextrin, yellow. Powder form produced by roasting ~ dry starch at relatively high temperatures at low pH.	Highly converted hydrolysed starches incorporating residues of amylose and amylopectin which will incorporate some transglucosidation and repolymerisation	Yellow coloured and relatively soluble - especially when heated - in water.

1 Cyclodextrins and their derivatives have been used
2 extensively in pharmaceutical applications and details
3 may be found in a number of patent sources (e.g. Uekama
4 et al, 1989).

One important application of solid dose formulations is the application in rapid release oral dose (buccal melt) type formulations. These products have been described by Ohno et al (1999) in relation to their buccal type formulations and those of their competitors. The proposed advantage of the Ohno et al (1999) technology over their competitors is the capacity to make solid formulations that might disintegrate rapidly. The technology describes the use of a pharmaceutically active agent, erythritol, crystalline cellulose and a disintegrant.

Fast dissolving formulations have been described by Makino et al (1993) where they describe the use of an active ingredient, a carbohydrate and a barely sufficient amount of water to moisten the surface of particles of the said carbohydrate into a tablet form and a fast dissolving tablet obtained by this method. The carbohydrate fraction is defined as to include sugar, starch-sugars, lactose, honey, sugar alcohols and tetroses with tablets which are porous with excellent digestibility, solubility and adequate strength. It is stated that the carbohydrate to be employed must be 'soluble in water and does not adversely affect the active ingredient (for example, decomposition of the active ingredient)'. The disclosure concentrates on sugars as they would be expected to dissolve and disperse apart from the active ingredients in tablets without entrapment-type interactions upon hydration. The disclosed preference is to use 'sucrose, glucose, maltitol, xylitol, erythritol and so on' [sugar and sugar alcohols but no

mention of oligo- or polysaccharides]. Also mentioned are 'sugar, starch-sugars, lactose, honey, sugar-alcohols, tetroses, sucrose, coupling-sugars, fructooligosaccharides, palatinose and so on'. Sugars are elaborated as 'glucose, maltose, powdered syrup, starch syrup, isomerised sugar (fructose) and so on'. For lactose they elaborate as 'lactose, isomerised lactose (lactulose), reduced lactose (lactitol)'. For sugar alcohols they include sorbitol, mannitol, reduced malt syrup (maltitol), reduced starch saccharides, xylitol, reduced palatinose and so on'. Tetroses are defined as obtained from glucose fermentation.

Zydis is a technology platform owned by R P Scherer where fast dissolving formulations are manufactured by blending and dissolving an active ingredient with a polymer, sugar and other ingredients followed by freeze drying (lyophilisation or in the context of the patent description 'sublimation'). Although some authors have proposed that freeze dried formulations are problematic and have proposed solvent extractable matrices or matrices incorporating solvent sublimation to add advantage (Gregory et al, 1983; Gole et al, 1994) the Zydis technology is still popular. Gregory et al (1983) and Gole et al (1994) discuss the use of dextrins in their (sublimed/freeze dried) delivery matrices but do not define which type of dextrin which is very confusing in view of the very different chemistries and physical properties of different dextrins. The authors do not have interests in tablet production (by compression) *per se*. In reality, only some dextrins would impart desirable characteristics (forming the

appropriate structure and melt type characteristics) in these freeze dried matrix types whilst others would be detrimental. For example, the dextrins present in maltose syrups have a very low molecular weight and would be very different (size, shape, structure, solubility, reducing power, rheology, digestibility etc.) from dextrins produced from very limited (acid or α-amylase) hydrolysis of native starches. In fact, the only example Gregory (1983) cite is 'dextrin' (not type, source etc.) while the Gole et al (1994) application is based on (exemplified by) maltodextrin (which is generated by α-amylase but not β-amylase as previously discussed). It is apparent in these patents that the applicants do not understand the breadth of different chemical species and properties in different types of dextrins. Different dextrins have different properties and chemistries.

According to the invention, there is provided a solid unit dose product comprising an active agent and a carrier for the active agent, wherein the carrier comprises β-limit dextrin.

In a preferred embodiment of the invention, the unit dose product is a pharmaceutical product such as, for example, a fast melt or slow melt tablet, a freeze dried matrix, a wafer, a pellet or the like. Suitably, therefore, the unit dose product may be a capule comprising a pharmaceutical formulation enclosed within a hard or soft shell. In such cases, either or both of the shell and the enclosed formulation may include β-limit dextrin.

In this specification, the terms "pharmaceutical product" and "pharmaceutical preparation" should be understood to include therapeutic and prophylactic pharmaceutical products as well as health promoting agents such as vitamins, minerals, herbal remedies, proteins, amino acids and the like.

The invention also relates to a particulate product comprising an active agent and a carrier for the active agent, wherein the carrier comprises β-limit dextrin. In this specification, the term " particulate product" should be understood to include powders, granules and flakes. Typically, the particulate product is derived from pulverised freeze dried matrices or spray dried material. Suitably the particulate product is a pharmaceutical product. In one embodiment of the invention, the particulate product is an inhalation-type product. The invention also relates to a liquid formulation comprising an active agent and a dispersing agent for the active agent, wherein the dispersing agent is β-limit dextrin. Typically, the liquid formulation is a pharmaceutical formulation such as, for example, a tincture, however, non-pharmaceutical liquid formulation are also envisaged.

The invention also relates to the use of β-limit dextrin as an excipient in pharmaceutical formulations, either as a sole excipient or as one of a plurality of excipients. The invention also relates to the use of β-limit dextrin as a dispersant in liquid pharmaceutical and non pharmaceutical formulations. The invention

also relates to the use of β-limit dextrin as an excipient in fast-melt solid unit dose pharmaceutical products.

The invention also relates to the use of β-limit dextrin as a disintegrant in solid products such as pharmaceutical and detergent formulations and the like. The invention also relates to liquid formulations reconstituted from a solid formulation of the invention.

Melt Formulations

These are rapidly disintegrating formulations which are intended to be dissolved very rapidly in the buccal cavity (mouth). Generally these formulations lack physical strength.

Use of β-limit dextrins in freeze dried matrices and tablet (including melt) type formulations

These have not been defined elsewhere. As discussed above, freeze dried matrices have been described (containing 'dextrins') but do not incorporate the use of β-limit dextrins. Furthermore, tablet formulations with melt or slow release type formulations have not been described at all where β-limit dextrins have been incorporated. The unique characteristics of β-limit dextrins in freeze dried matrices and tablets are

unexpected and surprisingly as presented later in this application.

Powder formulations incorporating β-limit dextrins

These molecules can be formed from dried matrices (e.g. from pulverised freeze dried matrices or from spray dried material). We have found that active agents can be incorporated into these matrices before drying or blended together subsequently. These applications are discussed below. This material clearly has applications in tablets (above), sachets etc. and as an inhalation type (pulmonary) carrier as the material is quite 'sticky' when hydrated.

Liquid formulations incorporating β-limit dextrins

This dextrin is highly soluble. Also, because of the removal of exterior chains (of amylopectin) the product cannot retrograde (recrystallise) easily if at all from solution. This makes the product very stable in solution and appropriate as a dispersing component in liquid pharmaceutical (and non-pharmaceutical) preparations.

The invention will be more clearly understood from the following description of some embodiment thereof, given by way of example only, with reference to the accompanying Figures in which:

Figure 1 is a graph illustrating the rheological properties of a product according to the invention; and

Figures 2 and 3 illustrate the dissolution properties of a number of products according to the invention

β-limit Dextrin Production

These dextrins may be produced from starches of different botanical origins and different genetic modifications, chemical, enzymatic or physical derivatives. Since all the amylose is converted to maltose, it is much more cost effective to use high amylopectin ('waxy type') starches where there is a higher proportion of amylopectin - the origin of the β-limit dextrin.

The dextrin may be produced by a number of routes and the following method does not exclude material produced by other routes nor using other sources of enzyme or processing conditions.

The dextrin is produced in conjunction with maltose from the α-glucan hydrolysis. In the method described below, the maltose is removed by dialysis leaving pure dextrin. However, the maltose could be left in the product as an option (to impart sweetness and novel functionality).

Waxy maize starches (*c.* 25g) were dissolved in 500ml acetate buffer (0.02M, pH 4.8) at 100°C for at least 1 hour. After cooling to room temperature, crystalline sweet potato β-amylase (5×10^3 units, Sigma A-7005) was added and the mixture was thoroughly mixed. The mixture

were then transferred into dialysis tubing (Visking code DTV 12000.13.000) and incubated for 36 hours at 37°C under dialysis against the same buffer, which was renewed three time during the first 3 hours and twice afterwards. After the reaction had been terminated by heating the mixture for 10 mins at 100°C, the coagulated protein was removed by centrifugation, and then ethanol were added to the solution. The resulting precipitate was collected by centrifugation, dissolved in water (250ml) and then re-precipitated by the addition of ethanol. The precipitate recovered on centrifugation was finally dissolved in water and then dried (below).

Drying Tests

Dextrin alone

The dextrin was dried using freeze drying and spray drying (including use of small pilot scale Büchi mini spray dryer model B-191). The spray dried material is a fine powder with good flow characteristics. The freeze dried material makes a fine lyophilised matrix. This may be milled to a powder which tends to be a little electrostatic in character.

Dextrin Characterisation

The product of β-amylase hydrolysis was analysed by gel permeation chromatography (GPC, using Sepharose CL-2B gels) according to Karkalas and Tester (1992) before and after dialysis (to remove maltose). Accordingly the

retention time and molecular weight of the dextrin was smaller than the native amylopectin (with maltose present prior to dialysis). This confirms that the native amylopectin molecules were selectively hydrolysed.

Rheological Properties

To prove that the rheological properties of a drug in solution with a sugar (glucose) or the β-limit dextrin are different in terms of interactions the following experiment was conducted.

Samples of theophylline and either glucose or the β-limit dextrin were dispersed in water (to give a concentration of 1% theophylline, w/w and either 1% with respect to glucose or beta-limit dextrin, w/w) within sealed screw capped tubes. These were sealed and mixed and kept in a 25°C water bath. The viscosity was immediately determined using a Brookfield DV-III Viscometer (Brookfield Engineering Laboratories, INC., USA) fitted with a cone and spindle CP-40 system (2.4cm dimension and 0.8° angle) with a thermostatically controlled temperature of 25°C. A silicon viscosity standard (96.2mPas at 25°C) from Brookfield was used for calibration.

Enzyme digest with or without dialysis to remove maltose.

The properties of formulations containing the dextrin which have none, some or all of the maltose remove (howsoever) differ in their properties. These are considered below.

Applications

Examples

1. Tablet Formulations

It was found that the dextrin could be tableted directly to form products with different drugs. The following examples exemplify this.

a. Direct compression

β-limit dextrin was prepared from waxy maize starch and was spray dried to form a fine powder.

b. Granulation

Samples (15g) of the β-limit dextrin (dried by freeze drying) was wet massed with 5ml water using an FP296 mixer (Kenwood Ltd, UK). Granules were then spread evenly over a drying tray and dried overnight at 60°C. Dried granules were passed through a 300μm mesh to produce a free-flowing powder.

Two formulations were produced using the same water-soluble drug but different types of additional tabletting excipient since the tablet release matrix

(first) formulation was not easily tabletable with drug alone (as friable tablets were produced). Each formulation was then tested using a standard USP II paddle dissolution apparatus (ST-7 model, Caleva Ltd, UK) at 37°C in 1000ml water (λ_{max} propranolol·HCl = 298nm).

Formulation 1. β-limit dextrin, hydrophilic excipient and tablet release formulation

Formulation:

40% β-limit dextrin

20% Microcrystalline cellulose (Avicel 101)

20% Lactose

20% Propranolol·HCl

The formulation was mixed for 30 minutes using an orbital Turbula™ mixer (Glen-Creston Ltd, Middlesex, UK). The resultant mixture was then tabletted with a 7.95mm concave punch and die set using an E2 single punch tablet press (BWI-Manesty Ltd, Liverpool, UK).

Tablet properties made according to hydrophilic tablet Formulation

No.	Weight (mg)	Thickness (mm)	Hardness (N)	Diameter (mm)
1	194.9	3.99	36	7.95
2	201.6	4.09	40	7.94
3	181.6	3.79	28	7.93
4	201.0	4.06	46	7.93
5	179.6	3.75	25	7.93
6	190.7	3.95	32	7.96
7	177.9	3.73	32	7.94
8	194.3	4.00	24	7.94
Mean	190.2	3.92	33	7.94
SD	± 9.4	± 0.14	± 7	0.01

Formulation 2. β-limit dextrin, hydrophobic excipient and tablet release formulation

Formulation:

50% β-limit dextrin

25% Emcompress® (Dibasic calcium phosphate)

25% Propranolol·HCl

The components were mixed and compressed as with the previous formulation (1).

Tablet properties made according to hydrophobic tablet formulation

No.	Weight (mg)	Thickness (mm)	Hardness (N)	Diameter (mm)
1	205.0	3.91	<10	7.94
2	192.9	3.72	<10	7.94
3	197.4	3.85	<10	7.94
4	199.2	3.78	<10	7.94
5	199.9	3.76	<10	7.96
6	194.0	3.74	<10	7.94
7	193.7	3.65	<10	7.96
8	197.4	3.83	<10	7.97
Mean	197.4	3.78	<10	7.94
SD	± 4.0	± 0.08		0.01

Better weight uniformity is obtained indicative of improved powder flow. Low hardness may be improved by adding a compression binding agent.

2. Dried matrices

Solutions/suspensions containing the dextrin and theophylline (e.g. 10% with respect to the dextrin and 0.1% with respect to theophylline) were freeze-dried where easily hydratable matrices were formed. These melt type formulations can also be milled to produce fine powders.

The matrices 'melted' or rather dissolved and dispersed exceedingly easily when water came into contact with them. It is evident that freeze-dried products could be made from this material.

3. Powder Formulations

These may be made from milling dried matrices (e.g. '2'). However, powders can also be made directly by for example spray drying.

Solutions containing the dextrin and theophylline (e.g. 10% with respect to the dextrin and 0.1% with respect to theophylline) were spray dried where very fine powders were prepared that disperse very easily upon hydration. These may be tableted (see above) or utilised in sachet type formulations. It is anticipated that pulmonary type delivery products could be made from small particles comparable or smaller than dimensions present in these powders.

4. Liquid Formulations

The β-limit dextrin was dissolved in water (for example a 10% solution) with theophylline (for example 0.1%). The solution was found to be very stable at room temperature and could be used as a liquid formulation for oral delivery of drugs and for parenteral administration.

5. Enhancement of drug solubility

It was noted that rather surprisingly the β-limit dextrin could facilitate the dissolution of drugs. There are many potential applications with respect to dispersing and solubilising insoluble compounds. The following example indicates that this is so.

6. Dialysis

It is also apparent that the material could be potentially used for intra-peritoneal dialysis if a low osmotic α-glucan is required. The product would potentially fulfil the need in this area provided by oligosaccharide type products like 'icodextrin' produced by ML Laboratories. The following example indicates that this is so.

7. Adhesions

Similarly to the icodextrin product discussed above, it is anticipated that the material could function to prevent tissue adhesion. This is because as follows.

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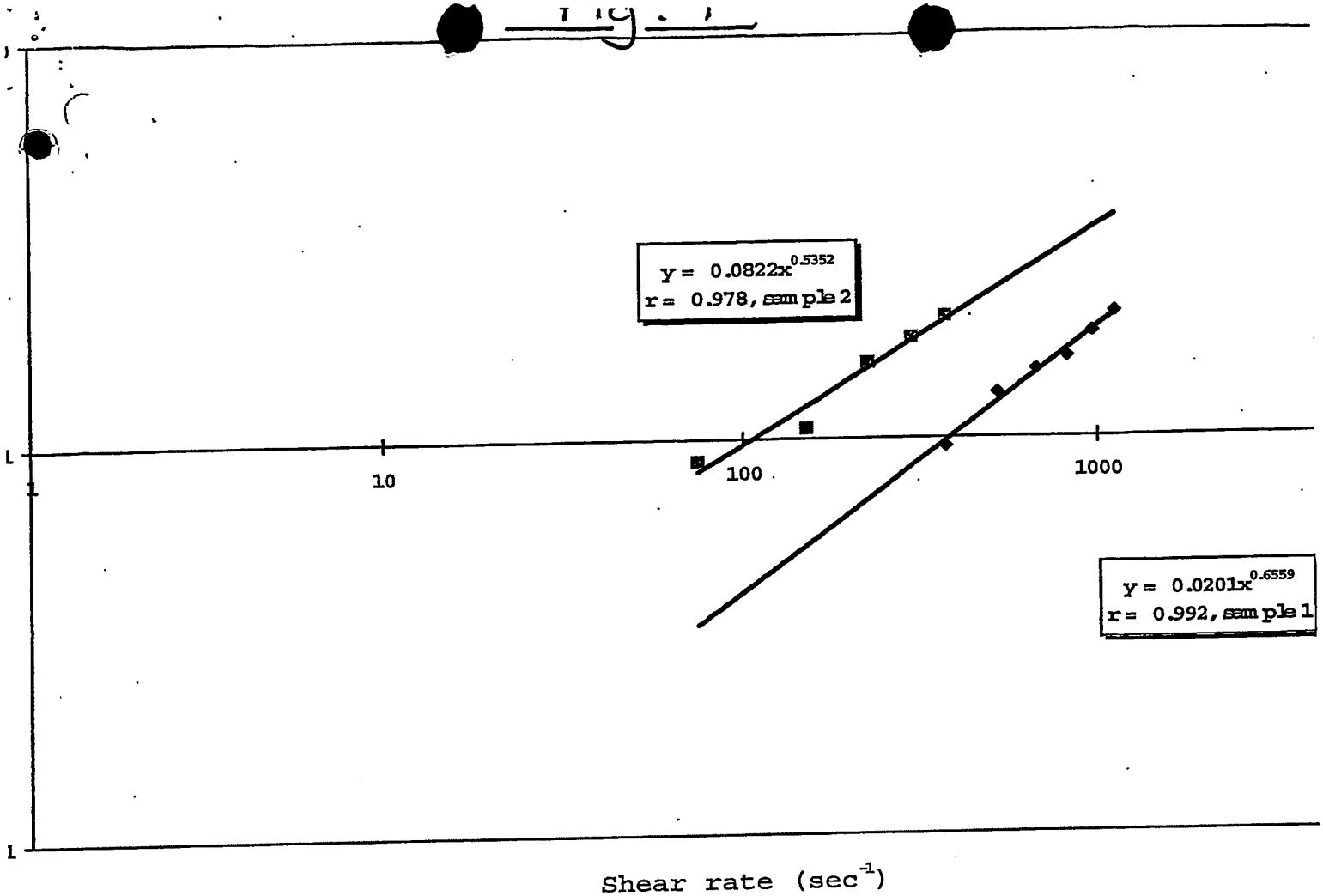
Yoshida, T., Ishige, Y., Matsudaira, M. and Takahashi, T. (1989) Branched dextrin production and compositions containing same. US Patent 4,840,807.

Fig. 1



Sample 1: glucose solution contains 1% glucose and 1% theophylline
Sample 2: beta-limit dextrin solution contains 1% beta-limit dextrin and 1% theophylline).

Fig. 2

Dissolution Data

Formulation 1.

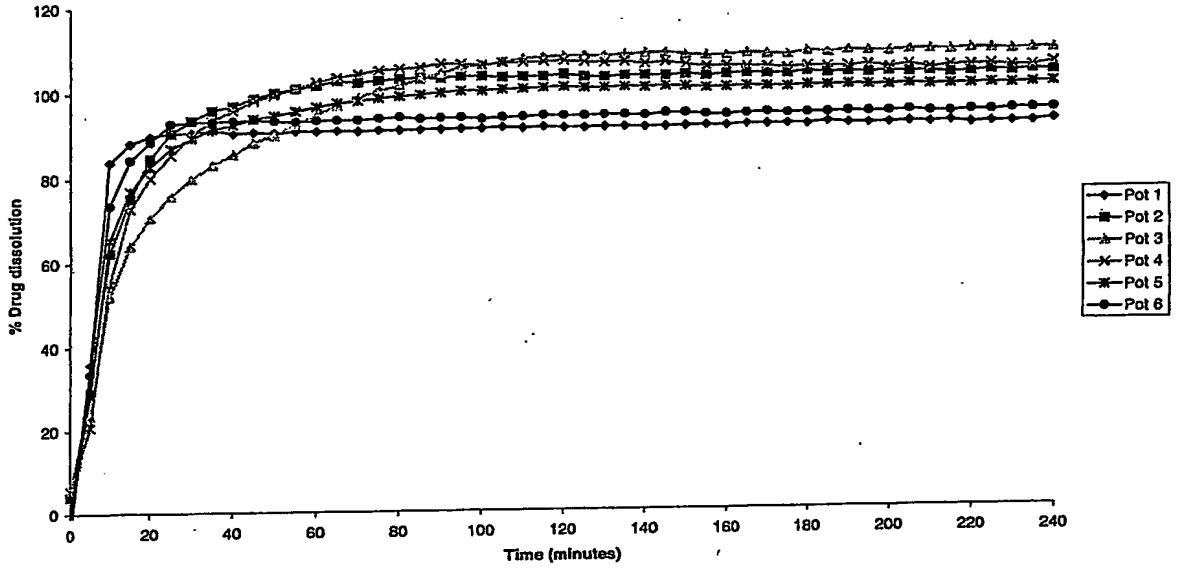


Fig. 3

Formulation 2.